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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/167,516	10/06/1998	MARTIN A. CHEEVER	920010.448C8	1422

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 01/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/167,516	CHEEVER ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 7-9,11 and 12 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 7-9,11 and 12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claim 10 has been canceled. Claim 12 has been amended. Claims 7-9 , 11 and 12 are pending and under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. The rejection of claim 12 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

Claim 12 has been amended to read on a fusion protein with a peptide or a polypeptide. The specification and claims as filed do not provide support for the claimed subject matter including a fusion protein. It is noted that the amendment of October 20, 2003 deleting the limitation "having immunogenic properties" is broader in scope than the previously amended claim which was also rejected under new matter.. The specification contemplates only the expression of the her-2/neu polypeptide fused to thioredoxin reductase to increased stability of the recombinant protein in an E coli host cell, "While thioredoxin reductase has been reported to stabilize and solubilize other heterologous proteins expressed in E. coli. it did not appear to offer any significant advantage for human HER-2/neu polypeptide expression in E. coli. While a significant proportion of the trxA-HER-2/neu polypeptide fusion protein was soluble, a majority was expressed in inclusion bodies. The fusion protein was also subjected to .degradation during expression in E. coli. The presence of the thioredoxin reductase fusion partner may, however, stabilize the protein during purification. The availability of monoclonal antibodies to thioredoxin reductase provides a convenient marker to follow during purification." (page 39, lines 1-13). This is not adequate support for an amendment which contemplates a method of treatment comprising the administration of a nucleic acid or a cell expressing said nucleic acid, wherein the nucleic acid encodes a fusion protein. The thioredoxin reductase was not used as an immunogenic protein in a warm-blooded animal, but used to enhance the stability of the expressed protein in the environment of an E coli host cell.

Further, the amended claims are now a genus claim which encompass said immunogenic fusion partnersApplicant argues that6 "the subject specification contemplates fusion proteins wherein the additional peptide or polypeptide may or may not have immunogenic properties". However, applicant has failed to site page and line number, or a figure to support this allegation. The examiner has looked for support for the claimed polynucleotides encoding fusion proteins without success. Applicant argues that the prior Office action appears to be concentrated on only one embodiment, however, only one example of a fusion with thioredoxin reductase was taught by the specification as a potential improvement for the expression of the protein in E coli, and no evidence can be found that a contemplation of a larger genus of fusion proteins was part of the invention.

4. The rejection of claims 7-9, 11 and 12 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons of record. The instant claims are drawn to methods or eliciting or enhancing an immune response to Her-2/neu comprising the administration of a nucleic acid molecule or a viral vector to a warm blooded animal, administering a transfected antigen presenting cell to a warm blooded animal and administering an infected antigen presenting cell to a warm blooded animal.

The specification states on page 32, line 17 to page 33, line 7 that vectors for the delivery of the nucleic acids of the invention include recombinant viral vectors including retro viruses, adenovirus, pox virus, naked DNA, and nucleic acids associated with polycationic molecules and liposomes. The claims are clearly intended to encompass methods of gene therapy. However, the specification is not enabling for gene therapy as a method of eliciting or enhancing an immune response against her-2/neu.

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene

therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that as of 1995, (two years after the priority date for the instant application) clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that in 1995, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that in 1995 current data regarding the level and

consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

Regarding the first full paragraph at the top of page 7 of the response, the examiner would like to point out that Office actions are done to be in consensus with examiners and supervisors of examiners within the 1642 art unit as well as with related art units.

Applicant argues that the instant claims do not encompass gene therapy because the immunization with DNA and viral vectors is not gene therapy because the purpose of gene therapy is to induce a sustained expression of a protein. Applicant maintains that they are drawn to eliciting or enhancing an immune response to HER-2/neu protein, and as such does not is not subject to the enablement rejection which centers on the lack of sustained expression of the desired protein. This has been considered but not found persuasive. In order to use the claimed method, the instant claims must produce an efficacious immune response, without undue experimentation. The specification provides evidence that the administration of the intracellular portion of the Her-2 protein produces a cellular immune response, However, in light of the unreliability of the art which teaches that issues relating to the adequate expression of proteins in vivo have not been resolved, one of skill in the art would be subject tot undue experimentation in order to carry out the claimed methods wherein the immune response which was generated produced an efficacious effect in a patient. Because of the unreliability of the art, it could not be assured that even a transient expression of the protein would be achieved to the extent which would be necessary to generate an efficacious immune response. With regard to retroviruses, Verma teaches that cells transfected ex vivo and administered to mice experience a

transcriptional shut-off that cannot be explained. It is noted that claim 8 is specifically drawn to transfected cells ex vivo and administering said cells.

Further, it is noted that gene therapy is defined by the National Library of Medicine Thesaurus as "the introduction of new genes into cells for the purpose of treating disease by restoring or adding gene expression" (www.gateway.nlm.nih.gov, visited 01/23/04). This supports the rejection based on gene therapy because the introduction of any polynucleotide, encoding a protein for purpose of treatment can be considered gene therapy according to the definition supplied.

Applicant argues further that the Verma et al reference provides evidence that supports the successful induction of an immune response with the statement that "host immune reactions" are a problem in gene therapy procedures. This has been considered but not found persuasive. Verma states on page 239, third column that "Most of the current gene-therapy approaches make use of the second category of viral vectors. Importantly, the viruses used have all been disabled of any pathogenic effects. The use of viruses is a powerful technique, because many of them have evolved as specific machines to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempt. to deliver genes in viral vectors have been confronted by these host responses" The immune response against the viral vector has no nexus with an immune response against a human protein expressed by said viral vector. It is noted that Verma states that humans have an immune system to fight off viruses. However, one of skill in the art would recognize that the parameters governing the recognition and mounting of an immune response against a viral protein would not have a nexus to an immune response against a human protein, because the immune response is governed by the discernment between self and non-self peptides. First, humans would have memory T-cells and memory B-cells against viral antigens which could be immediately stimulated by a small amount of viral protein. It is noted that the claims are drawn in part to the elicitation of the immune response d novo, requiring that an immune response be generated where no reactive T-cells or B-cells were previous present within the host. Second, even in the event of a de novo immune response, a viral peptide or protein would be perceived by the human immune system to be "non-self", whereas the recognition of human proteins is much more complex, moderated by such factors as the deletion of highly reactive T-cells in the spleen and the induction of anergy and peripheral tolerance.

Thus, one of skill in the art would recognize that it would be relatively easy for a minute amount of viral protein to trigger an immune response in a human infected therewith due to the fact that tolerance and anergy would not have to be overcome and due to the fact that memory T and B cells would already be present from previous exposures to the antigen or to a cross-reacting antigen. However, it is unclear if enough expression of the claimed polynucleotides could be attained and presented to the immune system to induce an efficacious immune response against the Her-2/neu protein.

5. All other rejections and objections as stated in the previous Office action are withdrawn.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is **(571) 272-0828**. The examiner can normally be reached on Monday through Friday from 9 am to 6:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.

Primary Examiner, Group 1642

January 23, 2004